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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,921	09/24/2001	Didier Raoult		3015

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EXAMINER	
BASKAR, PADMAVATHI	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 05/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,921	RAOULT ET AL.	
	Examiner	Art Unit	
	Padmavathi v. Baskar	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/18/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,10,11,15,25 and 29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,10, 11,15,25 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/28/04 has been entered.

Amendment

2. Applicant's amendment filed on 11/10/ 04 is acknowledged.

Status of Claims

3. Claims 6-9, 12-14, 16-24 and 26-28 are canceled.

New claim 29 has been added.

Claims 1, 11 and 15 have been amended.

Claims 1-5, 10, 11, 15, 25 and 29 are pending and are under examination in the application.

Claim Rejections - 35 USC 112, first paragraph withdrawn

4. In view of submission of appropriate Declaration for the deposit of the CNCM I-2202 and CNCM I-2411, the rejection under 35 USC 112, first paragraph is withdrawn.

Claim Rejections - 35 USC 102 maintained

5. The rejection of claims 1-5 and 10 under 35 U.S.C. 102(b) as being anticipated by Schoedon et al 1997 is maintained as set forth in the previous office action.

The Claims are drawn to a bacterium responsible for Whipple's disease, isolated and established in culture such that the bacterium reproducibly multiplies over time, wherein the bacterium is *Tropheryma whippelii,* said bacterium isolated and obtained from a culture of human fibroblasts after at least 2 months of incubation in a culture medium based on MEM.

Schoedon et al disclose isolation of *Tropheryma whippelii* bacterium (see Journal Infectious diseases, 176; 672-677) responsible for Whipple's disease (see abstract) from biopsy material obtained from a patient. The bacterium is cultured in medium containing (see figure1) deactivated mononuclear phagocytes (see page 673, right column, under inoculation of cultures) and thus read on claims 1 and 2. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated from PMNC read on claims 3-5 and 10 because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention.

Recitation of "established in culture such that the bacterium reproducibly multiplies over time" is viewed as a process limitation. Where a claim is rejected over a prior art product that is identical, although produced by a different process, the burden is upon the applicants to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Thorpe*, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). *In re Marosi*, 218 U.S.P.Q. 289, 293-293 (C.A.F.C. 1983). *In re Best*, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). *In re Brown*, 173 U.S.P.Q. 685, 688 (C.C.P.A. 1972). Further, the structure of the bacterium obtained by the prior art and the claimed bacterium are the same because both of them are *Tropheryma whippelii.*

In claim 2 " bacterium obtained from a culture of human fibroblasts after at least 2 months of incubation in a culture medium based on MEM" is also considered as a process limitation. The product of the prior art and the claimed product are the same because the claimed product produced in human fibroblast does not distinguish the product of the prior art in the absence of other structural characteristics. The patentability is based on the product itself. The patentability of a product does not depend upon its process. If the product of the claim is the same as the product of the prior art, the claim is unpatentable even though the product was made by a different process. Where a product claim is rejected over a prior art product that appears to be identical, although produced by a different process, the burden is upon the applicants to provide evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Thorpe*, 227 U.S.P.Q. 964, 966 (Fed. Cir. 1985). *In re Marosi*, 218 U.S.P.Q. 289, 293-293 (C.A.F.C. 1983). *In re Best*, 195 U.S.P.Q. 430, 433 (C.C.P.A. 1977). *In re Brown*, 173 U.S.P.Q. 685, 688 (C.C.P.A. 1972). The prior art anticipated the claimed invention.

Applicants' arguments filed on 1/28/04 has been fully considered but they are not deemed to be persuasive.

Applicant states that Schoedon studies carried out on primary cultures of human blood monocytes. As discussed in the present specification at page 2, lines 19-24, such a culture cannot be used as a basis for establishing the bacterium in culture in such a way that it can be multiplied because the mean lifetime of monocytes is only 30 days, which is insufficient in view of the doubling time of the bacterium. In particular, since human blood monocytes do not multiply, the primary culture described in Schoedon cannot be used as a basis for multiplication of the bacterium. Further, Raoult et al (The New England Journal of Medicine, Vol. 342, No. 9,pp. 620-625 2000, provided with the IDS filed May 15, 2002) indicate that the isolated bacterium described in Schoedon "could not be sub-cultured" (p. 620, col. 2) in culture such that the bacterium reproducibly multiplies over time. Thus, Schoedon does not teach a bacterium isolated and established. In addition, Schoedon is not an enabling disclosure. In particular, as described in Maiwald et al (Journal of Infectious Diseases, Vol. 188, pp. 801-808 2003,copy attached) "Cultivation of *Tropheryma whippelii* bacteria that has been established in culture such that it reproducibly multiplies over time from Cerebrospinal Fluid" the finding of Schoedon of the propagation of bacteria could not be confined in subsequent studies (Maiwald et al., p. 802, col. 1, lines 4-9, and p. 805, col. 2, lines 2-5). This was further confirmed by one of the authors of Schoedon, Martin Altwegg, who indicated in a 1999 article by Hinrikson et al (International Journal of Systematic Bacterioloa, Vol. 47, pp. 1701-1706), which was submitted with the IDS filed May 15, 2002, that the relationship between clinical manifestations of Whipple's disease and different infecting strains of *Tropheryma whippelii* has not been studied mainly because of the absence of reliable cultures, Schoedon et a1. 1997. In fact, the summary of this article on p.1701 refers to *Tropheryma whippelii* as "an uncultivated causative

agent of Whippie's disease " (emphasis added). For at least these reasons, Schoedon does not teach the invention of claim 1, or claim 2 that depends from claim 1. Applicant states that claim 4 is directed to an isolated antigen of the bacterium according to claim 1 Schoedon does not teach an isolated antigen of the *Tropheryma whippelii.* Therefore, the rejection of claim 4 should also be withdrawn.

The examiner understands that first isolation of *Tropheryma whippelii* using human macrophages, inactivated with interleukin was reported in 1997 by Schoedon et al. Subsequently Muller et al 1999 (see below under new rejections) cultivated the bacteria in IL4 deactivated macrophages and propagated in U937 cells (see abstract). Further, Drancourt 1999 (see below (see below under new rejections) discloses that *T.Whippelii* is isolated from two heart valves sampled from two patients deactivated by a combination of dexamethasone, interleukin-4 (1L-4) and IL10 (see Table 1). They were subsequently cultivated on one human line of monoblast SigM5. Therefore, it appears that *T.Whippelii* is isolated and propagated in cell lines. Further, claims 3-5 and 10 do not distinguish the bacterium from the prior art as the art disclosed the same*Tropheryma whippelii.* Based on these reports it appears that Schoedon is an enabling disclosure. However, if applicant questions the enablement of the teachings of the prior art and Schoedon fail to put the public in possession of isolated and cultured *Tropheryma whippelii*, then an affidavit which questions the enablement of the teachings of the cited prior art should be submitted (MPEP: 2205). In the absence of evidence to the contrary, this rejection is maintained.

New Rejections

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Muller et al 1999 GASTROENTEROLOGY. Vol, 116, No. 4. Part 2, Abstract 910, 1999. (Abstract only). Claims have been discussed supra.

The prior art discloses *T.Whippelii* is isolated from interleukin-4 (1L-4) deactivated peripheral blood mononuclear cells (PMNC) of a patient with Whipple's disease, diagnosed by the presence of Periodic-acid-schiff (PAS) positive macrophages. Additionally, *T- Whippelii* can replicate in IL4 treated monocytic U937 cell line (see abstract) and thus the bacteria multiply over the time. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated from PMNC read on claims 3-5 and 10 because these claims do not distinguish the bacterium from the prior art as the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention.. The prior art anticipated the claimed invention.

8. Claims 1-5 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Drancourt 1999 Presse Medicale, Vol. 2: No. 8, February 27. 1 999, pp. 435-439 (See translated article).

Claims have been discussed supra.

The prior art discloses *T.Whippelii* is isolated from two heart valves sampled from two patients, deactivated by a combination of dexamethasone, interleukin-4 (1L-4) and IL10 (see Table 1) Further, bacteria were cultivated or propagated in human cell line, monoblast SigM5 (see page 8, bottom of the page) and thus the bacteria multiply over the time. Since isolated bacteria is routinely used as an antigen in the art, the bacteria isolated and propagated read on claims 3-5 and 10 because these claims do not distinguish the bacterium from the prior art as

the art disclosed the same *Tropheryma whippelii.* The prior art anticipated the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections, set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claims 11,15, 25 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoedon et al 1997 (see Journal Infectious diseases, 176; 672-677) or Muller et al 1999 Gastroenterology. Vol, 116, No. 4. Part 2, Abstract 910,1999. or Drancourt 1999 Presse Medicale, Vol. 2: No. 8, February 27. 1999, pp. 435-439 in view of 394 in view of Harlow and Lane 1986 , Cold Spring Harbor Laboratory 1988, (chapter 14)

The claims are directed to a method for the in vitro diagnosis of diseases associated with infections caused by Tropheryma whippelii, comprising contacting serum or any other biological

fluid of a patient with a Tropheryma *whippelii* bacterium or antigen, said antigen or bacterium on a solid support and detecting an immunological reaction.

Schoedon et al 1997 Or Muller et al or 1999 or Drancourt 1999 as stated above teach an isolated *Tropheryma whippelii* bacterium or antigen associated with Whipple's disease. However, the prior art does not teach a method of diagnosis comprising contacting the serum or any other biological fluid with bacteria or antigen on a solid support and detecting the immunological reaction.

Harlow and Lane teach several immunoassays for detecting antibodies in a sample using antigen assays. These immunoassays are listed in Table 14.1 including the method for detecting antibody (see page 560-561, 563) using antigen. The method comprises contacting the antigen on a solid support with the test solution (i.e., serum, biological fluid etc) and detecting the antibody and antigen reaction (immunological reaction) using labeled secondary reagent.

An artisan of ordinary skill would have been motivated to use *Tropheryma whippelii* bacterium or antigen in an immunoassay for the in vitro diagnosis of diseases associated with infections caused by *Tropheryma whippelii* because Drancourt 1999 clearly suggests that isolation of *Tropheryma whippelii* opens the way to the production of antigen for immunological diagnosis (see page 9 of Drancourt 1999). Therefore, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to *Tropheryma whippelii* bacterium or antigen as taught by Schoedon et al 1997 Or Muller et al or 1999 or Drancourt 1999 in a routinely used immunoassay method for detecting antibodies as taught by Harlow and Lane because *Tropheryma whippelii* bacterium or antigen and the methodology for detecting the antibody are taught by these two prior arts. The claimed invention is prima facie obvious in

Schoedon et al 1997 Or Muller et al or 1999 or Drancourt 1999 in view of Harlow and Lane absent any convincing evidence to the contrary.

Remarks

12. Claims 1, 2, 4, 5, 11, 15, 25, and 29 are rejected.

Claims 3 and 10 that depend on rejected base claim are objected.

Claim 2, the abbreviation " MEM " is used without definition upon their first appearance in the claims.

Relevant Prior Art

13 The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

Pace et al, U.S.Patent 6,083,683

Pace et al teach a method or in a diagnostic immunoassay kit for the diagnosis of infection (Shigella) in a biological sample (i.e., serum or any other biological fluid) comprising contacting said biological sample with a bacterium or antigen or a fragment thereof having an enhanced antigenic property wherein said bacterium is harvested from a culture and detecting an antibody present in said biological sample binding to the *Shigella* bacterium or fragment thereof wherein said detecting is by means of an immunoassay ,wherein said immunoassay is a radioimmunoassay, enzyme-linked immunosorbent assay (ELISA,), fluorescent immunoassay, or fluorescence polarization immunoassay (FPIA). The immunoassay or a diagnostic immunoassay used micro titer plates (solid support) for binding bacteria or antigen, and a conjugate antibody. Thus, the art teaches immunoassays for diagnosing bacterial disease associated with bacteria using either bacterium or antigen of said bacterium.

Conclusion

14. Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform to the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The Right Fax number is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PMR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PMR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Padma Baskar Ph.D., whose telephone number is ((571) 272-0853. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 6.30 a.m. to 4.00 p.m. except First Friday of each bi-week.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Padma Baskar Ph.D.

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